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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/651,582	SOOD ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Amendments of September 11, 2006, have been received and entered in full. Claims 1-40 are pending. Claims 31-35 are withdrawn as being directed to non-elected subject matter. Claims 1-30 and 36-40 are under examination. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 9, 10, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothschild et al. (USPN 5,986,076).

With regard to claim 1, Rothschild et al. teach a method of detecting an analyte comprising the steps of:

a) anchoring said analyte to a nucleic acid template (see col. 36 lines 35-61, where the biotin is anchored to the primer nucleic acid);

(b) conducting a nucleic acid polymerase reaction to produce labeled polyphosphate, said reaction comprising the reaction of said template, a primer, at least one terminal phosphate-labeled nucleotide, and a nucleic acid polymerase (see col. 36 lines 35-61, where the PCR contains a biotin molecule on the 5' end of each complementary strand)

(c) analyzing said labeled polyphosphate (see col. 37 lines 20-25 and table, where the product is analyzed for disease).

With regard to claim 2, Rothschild et al. teach the primer is a nuclease resistant primer (see col.

36 lines 35-42, where the primer has biotin on the 5' end).

With regard to claim 3, Rothchild et al. teach the nucleic acid polymerase reaction further includes an enzyme having 3' --> 5' exonuclease activity (see col. 34 lines 11-12, where Taq polymerase is recited. Taq polymerase has 3'-5' exonuclease activity).

With regard to claim 5, Rothschild teaches further including the step of separating nucleic acid template not achored before said conducting step (see col. 36 lines 35-61, where the primer template complex is thermally separated from uncomplexed template nucleic acids).

With regard to claim 9, Rothschild teaches the analyte is DNA (see col. 36 lines 35-61).

With regard to claim 10, Rothschild teaches the analyte is anchored to said nucleic acid template by non-covalent binding, or by one or more covalent bonds (see col. 36 lines 35-61, where the biotin is anchored to the primer nucleic acid via a covalent bond).

With regard to claim 11, Rothschild teaches the nucleic acid polymerase is a DNA polymerase (see col. 34 lines 11-12, where Taq polymerase is recited. Taq polymerase is a DNA polymerase).

With regard to claim 13, Rothschild teaches the nucleic acid template and said primer are switched and it is said primer that is anchored to the analyte (see col. 36 lines 35-61, where the biotin is anchored to the primer nucleic acid and the primer hybridizes to the template).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 8, 16-26 and 36, 37, 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) in view of Williams (USPN 6,255,083).

The teachings of Rothschild are presented above.

Rothschild does not teach the limitations of claims 7, 8, 16-30 and 36, 37, 38 and 39.

With regard to claim 7, Williams teaches further comprising the step of characterizing said analyte (see col. 1-3, where genotyping or sequencing the target nucleic is characterizing the analyte).

With regard to claims 8 and 16, Williams teaches he detectable species is produced in amounts substantially proportional to the amount of analyte (see col. 1-3, where the amount of PPi released for sequencing is proportional to the starting amount of template to be sequenced).

With regard to claims 17 and 39, Williams teaches at least one terminal phosphate-labeled nucleotide includes four or more phosphate groups in the polyphosphate chain (see col. 5).

With regard to claim 18, Williams teaches the labels in at least one terminal phosphate-labeled nucleotide are enzyme-activatable labels selected from the group consisting of chemiluminescent compounds, fluorogenic dyes, chromogenic dyes, mass tags, electrochemical tags and combinations thereof (see col. 5).

With regard to claims 19 and 20, Williams teaches the terminal phosphate-labeled nucleotides carry distinct labels (see col. 1-3, where Williams teaches three types of dNTPs labeled on the gamma phosphate with different fluorescent labels).

With regard to claim 21, Williams teaches one or more additional detection reagents are added in said polymerase reaction of said conducting step, and said additional detection reagents are capable of a response that is detectably different from said labeled polyphosphate (see col. 1-3, where Williams teaches one ore more additional detection reagents i.e. other three types of dNTPs labeled on the gamma phosphate with different fluorescent labels are added in the reaction in the reacting step).

With regard to claim 22, Williams teaches at least one terminal phosphate-labeled nucleotides are deoxy nucleotides and carry different labels (see col. 1-3).

With regard to claim 23, Williams teaches wherein at least one terminal-phosphate-labeled nucleotide is represented by the formula:

$$B\text{-}S\text{-}Y\text{-}P_{(n)}\text{-}P\text{-}L$$

wherein P is phosphate (PO_3) and derivatives thereof, n is 2; Y is an oxygen or sulfur atom; B is a nitrogen-containing heterocyclic base; S is an acyclic moiety, carbocyclic moiety or sugar moiety; L is an enzyme-activatable label containing a hydroxyl group, a sulfhydryl group or an amino group suitable for forming a phosphate ester, a thioester or a phosphoramidate linkage at the terminal phosphate of a natural or modified nucleotide, and P-L is a phosphorylated label which preferably becomes independently detectable when the phosphate is removed (see Figure 2).

With regard to claim 24, Williams teaches wherein said sugar moiety is selected from the group consisting of 2'-deoxyribosyl (see Figure 2).

With regard to claim 25, Williams teaches wherein said base is selected from the group consisting of uracil, thymine, cytosine, guanine, (see Figure 2).

With regard to claim 26, Williams teaches wherein said enzyme-activatable label is a fluorogenic dye (see Figure 2 and col. 5 lines 30-31).

With regard to claims 36 and 37, Williams teaches detection of a single base differences (see col. 1-3, where Williams teach genotyping of the analyte. Genotyping constitutes the detection of single base differences in the template).

With regard to claim 38, Williams teaches detecting the labeled polyphosphate (see the abstract, where Williams detects the release fluorescently labeled PPi).

It would have been prima facie obvious to use the method of anchoring the analyte to the template as taught by Rothschild with the detection method as taught by Williams in order to have a

method where sequence information is produced continuously since Williams teach this is advantageous because the polymerases continually incorporate all four nucleotides into the nucleic acid chains and there is no loss of synchronization because single molecules are observed separately (see col. 1 lines 52-55). One of skill in the art would be motivated to use the use the method of anchoring the analyte to the template as taught by Rothschild with the detection method as taught by Williams so sequence information would be available without the need for a secondary assay to obtain genotype or sequence information.

4. Claims 4, 6, 14, 15 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) in view of Williams (USPN 6,936,702).

The teachings of Rothschild are presented above.

With regard to claim 6, Rothchild teaches at least one terminal phosphate-labeled nucleotide is substantially non-reactive to phosphatase (see col. 36 lines 35-45, where the PCR primers and the complementary strand of the PCR product contains a biotin at the 5' end. The biotin on the primers and product is not cleavable by phosphatase).

Rothschild does not teach all of the limitations of 4, 6, 14, 15 and 40.

Rothschild does not teach analyzing using a labeled polyphosphate and a phosphatase to produce a detectable species characteristic of the analyte and detecting the cleaved labeled phosphate.

With regard to claims 4, 6 and 40, Williams teaches the analyzing step includes (a) reacting said labeled polyphosphate with a phosphatase to produce a detectable species characteristic of said analyte and (b) detecting said detectable species (see col. 2-4).

With regard to claim 14, Williams teaches the primer and the template form a hairpin (see col. 6 lines 57-58).

With regard to claim 15, Williams teaches wherein said detectable species is detectable by fluorescence emission, (see col. 2-4).

It would have been prima facie obvious to use the phosphatase to cleave the labeled terminal phosphate for detection as taught by Williams in order to produce a detectable species (i.e. fluorescent PPi) from the labeled polyphosphate with the method of detecting an analyte as taught by Rothschild in order to produce a detectable species from the labeled polyphosphate since Williams teach that using a phosphatase will dephosphorylate fluorescent PPi and produce a detectable species (see col. 2-4). One of skill in the art would be motivated to use the use the phosphatase to cleave the labeled terminal phosphate for detection as taught by Williams in order to produce a detectable species (i.e. fluorescent PPi) from the labeled polyphosphate with the method of detecting an analyte as taught by Rothschild in order to produce a detectable species from the labeled polyphosphate.

5. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) in view of Williams (USPN 6,255,083).

The teachings of Rothschild are described previously.

Rothschild does not teach the nuclease resistant primer has a phosphorothioate linkage.

Nikiforov et al. teach a nuclease resistant primer with a phosphorothioate linkage (see col. 13, where Nikiforov discloses phosphorothioate nucleotides on a primer are for resisting exonulcease attack).

It would have been prima facie obvious to use the phosphorothioate linkage as taught by Nikiforov et al. with the method of detecting an analyte as taught by Rothschild in order to avoid nuclease degredation, since Nikiforov et al. using a phosphorothioate linkage prevents nuclease degredation of primers (see col. 13). One of skill in the art would be motivated to use the phosphorothioate linkage as taught by Nikiforov et al. with the method of detecting an analyte as taught by Rothschild to avoid nuclease degredation of the primers used in the method of detection.

6. Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) and Williams (USPN 6,255,083) as applied to claim 26 above and in further view of Mandecki (USPN 6,001,571).

The teachings of Rothschild and Williams are described previously.

Rothschild and Williams do not teach the enzyme activatable label is 5-bromo-4-chloro-3-indolyl phosphate as recited in claim 28 or the label is an alkaline phosphatase activated 1,2-dioxetane compound or a derivative thereof as recited in claims 29 and 30.

With regard to claims 28, 29 and 30, Mandecki teaches the phosphorylated label is a chromogenic moiety is 5-bromo-4-chloro-3-indolyl phosphate or an alkaline phosphatase activated 1,2-dioxetane compound or a derivative of 1,2-dioxetane (i.e. adamantly 1,2-dioxetane) (see col. 3 lines 63-67 and col. 4 lines 1-12, where Mandecki teaches a label for oligoculcoetides is a chromogenic moiety as recited in claims 28-30).

It would have been prima facie obvious to use 5-bromo-4-chloro-3-indolyl phosphate or an alkaline phosphatase activated 1,2-dioxetane compound or a derivative of 1,2-dioxetane (i.e. adamantly 1,2-dioxetane) as taught by Mandecki with the method of detecting an analyte as taught by Rothschild and Williams as this is a simple substitution of equivalents. One of skill in the art would be motivated to use 5-bromo-4-chloro-3-indolyl phosphate or an alkaline phosphatase activated 1,2-dioxetane compound or a derivative of 1,2-dioxetane (i.e. adamantly 1,2-dioxetane) as taught by Mandecki with the method of detecting an analyte as taught by Rothschild and Williams since the label taught by Williams and the label taught by Mandecki are exchangeable.

Furthermore, the motivation to make the substitution cited above arises from the expectation the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

7. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) and Williams (USPN 6,255,083) as applied to claim 26 above and in further view of Parker et al. (USPN 5,565,323).

The teachings of Rothschild and Williams are described previously.

Rothschild and Williams do not teach the enzyme activatable label is 5-bromo-4-chloro-3-indolyl phosphate as recited in claim 28 or the enzyme activatable label is a phosphorylated label and the fluorogenic moiety umbelliferyl phosphate as recited in claim 27.

> With regard to claim 27, Parker et al. teach a chromogenic moiety of 5-bromo-4-chloro-3-indolyl phosphate or 4-methyl umbelliferyl phosphate (see col. 8 lines 56-67 and col. 9 lines 1-9, where Parker et al. teaches a label for an oligonucleotide is a chromogenic moiety as recited in claims 27 and 28).
> It would have been prima facie obvious to use 5-bromo-4-chloro-3-indolyl phosphate or 4-methyl umbelliferyl phosphate as taught by Parker et al. with the method of detecting an analyte as taught by Rothschild and Williams as this is a simple substitution of equivalents. One of skill in the art would be motivated to use 5-bromo-4-chloro-3-indolyl phosphate or 4-methyl umbelliferyl phosphate as taught by Parker et al. with the method of detecting an analyte as taught by Rothschild and Williams since the label taught by Williams and the label taught by Parker et al. are exchangeable.
>
> Furthermore, the motivation to make the substitution cited above arises from the expectation the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

Response to Arguments

8. Applicants' arguments filed September 11, 2006, have been fully considered but they are not persuasive.

With respect to the 102 (b) rejections Applicants argue Rothschild does not conduct a nucleic acid polymerase reaction with "at least one terminal phosphate labeled nucleotide" and that Rothschild

uses normal dNTPs for the PCR not "terminal phosphate-labeled nucleotides." This argument is not persuasive because there is no requirement in instant claim 1 that the terminal phosphate labeled nucleotide be separate from the primer. Rothschild teaches a terminal phosphate-labeled nucleotide, where the biotin labeled primer meets this limitation.

With respect to all of the 103 (a) rejections Applicants argue that does not conduct a nucleic acid polymerase reaction with "at least one terminal phosphate labeled nucleotide" and that Rothschild uses normal dNTPs for the PCR not "terminal phosphate-labeled nucleotides." The teachings of Rothschild are clarified above making Applicants argument moot.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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11/06/08